Association Between Bortezomib Therapy and Eyelid Chalazia

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Bortezomib is a first-generation proteasome inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma both initially and in relapsed or refractory disease and for relapsed mantle cell lymphoma. A phase 3 trial is under way to investigate bortezomib use in newly diagnosed mantle cell lymphoma. Bortezomib, alone or with other agents, has shown promise in clinical trials of other disorders as well, including Waldenström macroglobulinemia, mucosa-associated lymphoid tissue lymphoma, and cutaneous T-cell lymphoma. Common adverse effects include gastrointestinal upset, fatigue, peripheral neuropathy, thrombocytopenia, and rashes. Recently, there have been case reports on a possible association between eyelid chalazia and bortezomib therapy.

Methods

Spontaneous reports of ocular adverse effects in association with bortezomib use were collected from the National Registry of Drug-Induced Ocular Side Effects (http://www.eyedrugregistry.com), which collects data from the FDA's Adverse Event Reporting System and from the World Health Organization's Uppsala Monitoring Centre. The National Registry of Drug-Induced Ocular Side Effects also collects data from spontaneous reports submitted directly to its website. Data gathered from the spontaneous reports included patient age and sex, a description of the adverse drug reaction (ADR), dosage and duration of bortezomib therapy until the onset of chalazia, concomitant drugs, and responses on dechallenge (the ADR abated with withdrawal of the drug) and rechallenge (the ADR recurred with reinstitution of the drug). In addition, a PubMed literature search was performed using the keywords bortezomib, chalazia, chalazion, ocular, side effects, adverse drug reaction, and vision.

Results

In total, 24 reports of chalazia occurring soon after the initiation of bortezomib therapy were collected from the reporting databases (14 case reports) and from the published literature (10 case reports). The number of cases grows to 57 if eyelid abnormalities or eyelid edema are included as criteria for chalazia in spontaneous reporting data. However, because reports of eyelid abnormalities or eyelid edema could not be verified...
as true chalazia, they were not included in the number of case reports herein. Of the 24 patients in our study, 8 were female, and 11 were male (the sex was unknown in 5). The mean age of patients was 61 years (age range, 37-79 years). The duration of bortezomib therapy before chalazia onset ranged from 26 to 428 days (mean, 98 days). Eight case reports had positive dechallenge responses, and 3 case reports had positive rechallenge responses. Eighteen case reports indicated multiple upper eyelid chalazia associated with bortezomib treatment. There was improvement or resolution of chalazia in every instance where bortezomib therapy was withdrawn. The mean bortezomib dose, administered subcutaneously or intravenously, was 1.3 mg/m², along with oral melphalan and prednisone. This dosage is the only one reported and is consistent with the recommendation from the package insert for bortezomib. These patients were frequently receiving multiple medications, most often rituximab, prednisone, melphalan, lenalidomide, dexamethasone, and antibiotics. There are no case reports from the spontaneous reporting databases of chalazia occurring in association with concomitant medications that patients received when administered bortezomib therapy.

Discussion

According to the World Health Organization’s classification for ADRs, the association between bortezomib use and the occurrence of chalazia is categorized as possible, primarily because dechallenge data available in 8 case reports indicate that each of the 8 patients recovered or improved when bortezomib therapy was discontinued. In addition, chalazia developed in 18 patients during slightly more than 3 months after the start of bortezomib therapy, indicating a strong temporal relationship. The 3 positive rechallenge case reports are also evidence of a possible relationship.

Two case series have described the occurrence of chalazia in patients treated with bortezomib. One clinical trial described 6 patients who developed conjunctivitis or chalazia when receiving bortezomib for Waldenström macroglobulinemia. There were no additional demographic data on these individuals. In another series, 6 patients who were receiving bortezomib for multiple myeloma developed chalazia a mean of 3.3 months after the initiation of therapy. Five of the 6 patients discontinued bortezomib therapy because of persistent chalazia despite surgical intervention in 4 of 6 patients. All patients reported improvement in the signs and symptoms of chalazia and less ocular discomfort after bortezomib therapy was discontinued. Three patients restarted bortezomib after initial discontinuation and had recurrence of chalazia. Edwards and Birrell described the “quality” of the chalazia as different from that of spontaneously occurring chalazia, with bortezomib-associated chalazia frequently requiring surgical intervention and being recalcitrant.

The biologic mechanism by which bortezomib could cause chalazia is unknown. Bortezomib may induce a systemic inflammatory response, as evidenced by frequent occurrences of rashes, systemic fatigue, and ocular inflammation in the form of chalazia. Bortezomib potentiates the release of the proinflammatory cytokines interleukin 6 (IL-6), tumor necrosis factor (TNF), and C-reactive protein (CRP). A tendency toward marked elevation of these proinflammatory cytokines was observed in a series of 11 patients after 2 or 3 cycles of bortezomib. One patient in that series developed cutaneous leukoclastic vasculitis in association with bortezomib use, with levels rising from 3 to 197 pg/mL for IL-6, from 25.5 to 195 pg/mL for TNF, and from 1.0 to 59.9 mg/mL for CRP (to convert CRP level to nanomoles per liter, multiply by 9.524). C-reactive protein is an acute-phase protein that is a reliable marker of systemic inflammation, and IL-6 is the primary inducer of CRP in hepatocytes. It is postulated that rashes occur in up to 18% of patients receiving bortezomib owing to the release of CRP, TNF, and IL-6 systemically. That prednisone therapy helps mitigate the skin reaction provides evidence that systemic inflammation has a strong role in the development of chalazia in patients receiving bortezomib. Many of the same receptors in the skin also reside within the eyelid. The skin and the eyelids, including the meibomian glands, may have in common certain molecules targeted by bortezomib.

Conclusions

Adverse drug reaction data on ocular adverse effects related to bortezomib use indicate that this proteasome inhibitor possibly causes chalazia, with most cases occurring within 3 months of the initiation of therapy. Withdrawal of bortezomib usually leads to resolution or marked improvement of chalazia. While the reliability of spontaneous reports is lacking owing to incomplete information and passive data collection, such reports can nonetheless serve as one of the first signals of a common ADR. It is not until millions of patients are exposed to a particular medication that rare ADRs come to light. A rarely occurring ADR is often not recognized in the clinical trial phase of a drug or in the early period after FDA approval. In the case of bortezomib, the development of chalazia soon after a patient begins to receive the drug can serve as a signal to physicians of a possible ADR. New reports of chalazia or other ocular adverse effects can be reported to the National Registry of Drug-Induced Ocular Side Effects.
ARTICLE INFORMATION

Submitted for Publication: June 17, 2015; final revision received August 6, 2015; accepted August 21, 2015.

Published Online: October 15, 2015.

Author Contributions: Drs Fraunfelder and Yang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acquisition, analysis, or interpretation of data: Both authors.

Drafting of the manuscript: Both authors.

Critical revision of the manuscript for important intellectual content: Both authors.

Administrative, technical, or material support: Fraunfelder.

Study supervision: Fraunfelder.

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Fraunfelder reported being director of the National Registry of Drug-Induced Ocular Side Effects. No other disclosures were reported.

Additional Contributions: Sharon Scott Morey (Mason Eye Institute) provided editing services in the preparation of the manuscript.

REFERENCES


